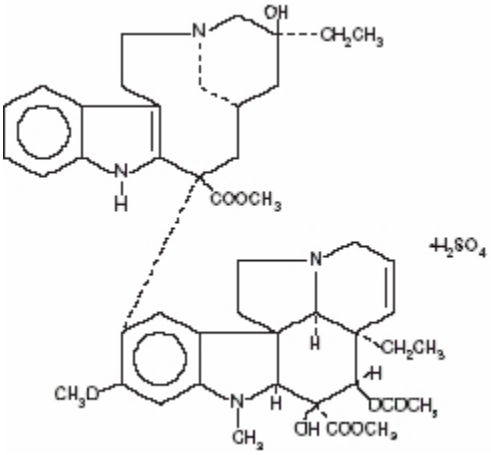
**VINBLASTINE SULFATE - vinblastine sulfate injection, powder, lyophilized, for solution**
Bedford Laboratories

**WARNING**
**Caution – This preparation should be administered by individuals experienced in the administration of vinblastine sulfate. It is extremely important that the intravenous needle or catheter be properly positioned before any vinblastine sulfate is injected. Leakage into surrounding tissue during intravenous administration of vinblastine sulfate may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis.**
**FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY.**
***See WARNINGS for the treatment of patients given intrathecal vinblastine.***

## DESCRIPTION

Vinblastine Sulfate for Injection USP is vincaleukoblastine, sulfate (1:1) (salt). It is the salt of an alkaloid extracted from *Vinca rosea* Linn., a common flowering herb known as the periwinkle (more properly known as *Catharanthus roseus* G. Don). Previously, the generic name was vincaleukoblastine, abbreviated VLB. It is a stathmokinetic oncolytic agent. When treated *in vitro* with this preparation, growing cells are arrested in metaphase.
Chemical and physical evidence indicates that vinblastine sulfate has the molecular formula $C_{46}H_{58}O_9N_4 \cdot H_2SO_4$ and that it is a dimeric alkaloid containing both indole and dihydroindole moieties.
The structural formula is as follows:




M.W.= 909.07
Vinblastine sulfate is a white to off-white powder. It is freely soluble in water, soluble in methanol, and slightly soluble in ethanol. It is insoluble in benzene, ether, and naphtha.
The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Vinblastine Sulfate for Injection USP contain 10 mg (0.011 mmol) of vinblastine sulfate, in the form of a white, amorphous, solid lyophilized plug, without excipients. After reconstitution with sodium chloride solution, the pH of the resulting solution lies in the range of 3.5 to 5.

## CLINICAL PHARMACOLOGY

Experimental data indicate that the action of vinblastine sulfate is different from that of other recognized antineoplastic agents. Tissue-culture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. *In vivo* experiments tend to confirm the *in vitro* results. A number of *in vitro* and *in vivo* studies have demonstrated that vinblastine sulfate produces a stathmokinetic effect and various atypical mitotic figures. The therapeutic responses, however, are not fully explained by the cytologic changes, since these changes are sometimes observed clinically and experimentally in the absence of any oncolytic effects.
Reversal of the antitumor effect of vinblastine sulfate by glutamic acid or tryptophan has been observed. In addition, glutamic acid and aspartic acid have protected mice from lethal doses of vinblastine sulfate. Aspartic acid was relatively ineffective in reversing the antitumor effect.
Other studies indicate that vinblastine sulfate has an effect on cell-energy production required for mitosis and interferes with nucleic acid synthesis. The mechanism of action of vinblastine sulfate has been related to the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage.
Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 3.7 minutes, 1.6 hours, and 24.8 hours, respectively. The volume of the central compartment is 70% of body weight, probably reflecting very rapid tissue binding to formed elements of the blood. Extensive reversible tissue

binding occurs. Low body stores are present at 48 and 72 hours after injection. Since the major route of excretion may be through the biliary system, toxicity from this drug may be increased when there is hepatic excretory insufficiency. The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes such as erythromycin. Enhanced toxicity has been reported in patients receiving concomitant erythromycin. (See PRECAUTIONS). Following injection of tritiated vinblastine in the human cancer patient, 10% of the radioactivity was found in the feces and 14% in the urine; the remaining activity was not accounted for. Similar studies in dogs demonstrated that, over 9 days, 30% to 36% of radioactivity was found in the bile and 12% to 17% in the urine. A similar study in the rat demonstrated that the highest concentrations of radioactivity were found in the lung, liver, spleen, and kidney 2 hours after injection.

**Hematologic Effects**

Clinically, leukopenia is an expected effect of vinblastine sulfate, and the level of the leukocyte count is an important guide to therapy with this drug. In general, the larger the dose employed, the more profound and longer lasting the leukopenia will be. The fact that the white-blood-cell count returns to normal levels after drug-induced leukopenia is an indication that the white-cell-producing mechanism is not permanently depressed. Usually, the white count has completely returned to normal after the virtual disappearance of white cells from the peripheral blood.

Following therapy with vinblastine sulfate, the nadir in white-blood-cell count may be expected to occur 5 to 10 days after the last day of drug administration. Recovery of the white blood count is fairly rapid thereafter and is usually complete within another 7 to 14 days. With the smaller doses employed for maintenance therapy, leukopenia may not be a problem.

Although the thrombocyte count ordinarily is not significantly lowered by therapy with vinblastine sulfate, patients whose bone marrow has been recently impaired by prior therapy with radiation or with other oncolytic drugs may show thrombocytopenia (less than 200,000 platelets/$mm^3$). When other chemotherapy or radiation has not been employed previously, thrombocyte reduction below the level 200,000/$mm^3$ is rarely encountered, even when vinblastine sulfate may be causing significant leukopenia. Rapid recovery from thrombocytopenia within a few days is the rule.

The effect of vinblastine sulfate upon the red-cell count and hemoglobin is usually insignificant when other therapy does not complicate the picture. It should be remembered, however, that patients with malignant disease may exhibit anemia even in the absence of any therapy.

**INDICATIONS AND USAGE**

Vinblastine sulfate is indicated in the palliative treatment of the following:

1. **Frequently Responsive Malignancies:**
   - Generalized Hodgkin’s disease (Stages III and IV, Ann Arbor modification of Rye staging system)
   - Lymphocytic lymphoma (nodular and diffuse, poorly and well differentiated)
   - Histiocytic lymphoma
   - Mycosis fungoides (advanced stages)
   - Advanced carcinoma of the testis
   - Kaposi’s sarcoma
   - Letterer-Siwe disease (histiocytosis X)

2. **Less Frequently Responsive Malignancies:**
   - Choriocarcinoma resistant to other chemotherapeutic agents
   - Carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy

Current principles of chemotherapy for many types of cancer include the concurrent administration of several antineoplastic agents. For enhanced therapeutic effect without additive toxicity, agents with different dose-limiting clinical toxicities and different mechanisms of action are generally selected. Therefore, although vinblastine sulfate is effective as a single agent in the aforementioned indications, it is usually administered in combination with other antineoplastic drugs. Such combination therapy produces a greater percentage of response than does a single-agent regimen. These principles have been applied, for example, in the chemotherapy of Hodgkin’s disease.

**Hodgkin’s Disease**

Vinblastine sulfate has been shown to be one of the most effective single agents for the treatment of Hodgkin’s disease. Advanced Hodgkin’s disease has also been successfully treated with several multiple-drug regimens that included vinblastine sulfate. Patients who had relapses after treatment with the MOPP program– mechlorethamine hydrochloride (nitrogen mustard), vincristine sulfate, prednisone, and procarbazine–have likewise responded to combination-drug therapy that included vinblastine sulfate. A protocol using cyclophosphamide in place of nitrogen mustard and vinblastine sulfate instead of vincristine sulfate is an alternative therapy for previously untreated patients with advanced Hodgkin’s disease.

Advanced testicular germinal-cell cancers (embryonal carcinoma, teratocarcinoma, and choriocarcinoma) are sensitive to vinblastine sulfate alone, but better clinical results are achieved when vinblastine sulfate is administered concomitantly with other antineoplastic agents. The effect of bleomycin is significantly enhanced if vinblastine sulfate is administered 6 to 8 hours prior to the administration

of bleomycin; this schedule permits more cells to be arrested during metaphase, the stage of the cell cycle in which bleomycin is active.

**CONTRAINDICATIONS**

Vinblastine sulfate is contraindicated in patients who have significant granulocytopenia unless this is a result of the disease being treated. It should not be used in the presence of bacterial infections. Such infections must be brought under control prior to the initiation of therapy with vinblastine sulfate.

**WARNINGS**

***This product is for intravenous use only. It should be administered by individuals experienced in the administration of vinblastine sulfate. The intrathecal administration of vinblastine sulfate usually results in death. Syringes containing this product should be labeled, using the auxiliary sticker provided to state ''FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."***

**Extemporaneously prepared syringes containing this product must be packaged in an overwrap which is labeled "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."**

**After inadvertent intrathecal administration of vinca alkaloids, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death. In a vey small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards.**

**There are no published cases of survival following intrathecal administration of vinblastine sulfate to base treatment on. However, based on the published management of survival cases involving the related vinca alkaloid vincristine sulfate, if vinblastine sulfate is mistakenly given by the intrathecal route, the following treatment should be initiated immediately after the injection:**

1. **Remove as much CSF as is safely possible through the lumbar access.**

2. **Insertion of an epidural catheter into the subarachnoid space via the intervertebral space above initial lumbar access and CSF irrigation with lactated Ringer's solution. Fresh frozen plasma should be requested and, when available, 25 mL should be added to every 1 liter of lactated Ringer's solution.**

3. **Insertion of an intraventricular drain or catheter by a neurosurgeon and continuation of CSF irrigation with fluid removal through the lumbar access connected to a closed drainage system. Lactated Ringer's solution should be given by continuous infusion at 150 mL/hour, or a rate of 75 mL/hour when fresh frozen plasma has been added as above.**

**The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150 mg/dL.**

**The following measures have also been used in addition but may not be essential:**

**Glutamic acid, 10 grams, has been given intravenously over 24 hours, followed by 500 mg three times daily by mouth for 1 month. Folinic acid has been administered intravenously as a 100 mg bolus and then infused at a rate of 25 mg/hour for 24 hours, then bolus doses of 25 mg every 6 hours for 1 week. Pyridoxine has been given at a dose of 50 mg every 8 hours by intravenous infusion over 30 minutes. Their roles in the reduction of neurotoxicity are unclear.**

**Usage In Pregnancy**

Caution is necessary with the administration of all oncolytic drugs during pregnancy. Information on the use of vinblastine sulfate during human pregnancy is very limited. Animal studies with vinblastine sulfate suggest that teratogenic effects may occur. Vinblastine sulfate can cause fetal harm when administered to a pregnant woman. Laboratory animals given this drug early in pregnancy suffer resorption of the conceptus; surviving fetuses demonstrate gross deformities. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Aspermia has been reported in man. Animal studies show metaphase arrest and degenerative changes in germ cells.

Leukopenia (granulocytopenia) may reach dangerously low levels following administration of the higher recommended doses. It is therefore important to follow the dosage technique recommended under the DOSAGE AND ADMINISTRATION. Stomatitis and neurologic toxicity, although not common or permanent, can be disabling.

**PRECAUTIONS**

**General**

Toxicity may be enhanced in the presence of hepatic insufficiency.

If leukopenia with less than 2,000 white blood cells/$mm^3$ occurs following a dose of vinblastine sulfate, the patient should be watched carefully for evidence of infection until the white-blood-cell count has returned to a safe level.

When cachexia or ulcerated areas of the skin surface are present, there may be a more profound leukopenic response to the drug; therefore, its use should be avoided in older persons suffering from either of these conditions.
In patients with malignant-cell infiltration of the bone marrow, the leukocyte and platelet counts have sometimes fallen precipitously after moderate doses of vinblastine sulfate. Further use of the drug in such patients is inadvisable.
Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin C and may require aggressive treatment, particularly when there is pre-existing pulmonary dysfunction. The onset may be within minutes or several hours after the vinca is injected and may occur up to 2 weeks following a dose of mitomycin. Progressive dyspnea requiring chronic therapy may occur. Vinblastine should not be readministered.
Care should be recommended in patients with ischemic cardiac disease.
*The use of small amounts of vinblastine sulfate daily for long periods is not advised*, even though the resulting total weekly dosage may be similar to that recommended. Little or no added therapeutic effect has been demonstrated when such regimens have been used. *Strict adherence to the recommended dosage schedule is very important*. When amounts equal to several times the recommended weekly dosage were given in 7 daily installments for long periods, convulsions, severe and permanent central-nervous-system damage, and even death occurred.
Care must be taken to avoid contamination of the eye with concentrations of vinblastine sulfate used clinically. If accidental contamination occurs, severe irritation (or, if the drug was delivered under pressure, even corneal ulceration) may result. The eye should be washed with water immediately and thoroughly.
It is not necessary to use preservative-containing solvents if unused portions of the remaining solutions are discarded immediately. Unused preservative-containing solutions shouId be refrigerated for future use.

**Information for Patients**
The patient should be warned to report immediately the appearance of sore throat, fever, chills, or sore mouth. Advice should be given to avoid constipation, and the patient should be made aware that alopecia may occur and that jaw pain and pain in the organs containing tumor tissue may occur. The latter is thought possibly to result from swelling of tumor tissue during its response to treatment. Scalp hair will regrow to its pretreatment extent even with continued treatment with vinblastine sulfate. Nausea and vomiting, although not common, may occur. Any other serious medical event should be reported to the physician.

**Laboratory Tests**
Since dose-limiting clinical toxicity is the result of depression of the white-blood-cell count, it is imperative that this count be obtained just before the planned dose of vinblastine sulfate. Following administration of vinblastine sulfate, a fall in the white-blood-cell count may occur. The nadir of this fall is observed from 5 to 10 days following a dose. Recovery to pretreatment levels is usually observed from 7 to 14 days after treatment. These effects will be exaggerated when preexisting bone marrow damage is present and also with the higher recommended doses (See DOSAGE AND ADMINISTRATION). The presence of this drug or its metabolites in blood or body tissues is not known to interfere with clinical laboratory tests.

**Drug Interactions**
Solutions should be made with normal saline (with or without preservative) and should not be combined in the same container with any other chemical. Unused portions of the remaining solutions that do not contain preservatives should be discarded immediately.
The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vinblastine sulfate has been reported to have reduced blood levels of the anticonvulsant and to have increased seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of vinblastine sulfate to this interaction is not certain. The interaction may result from either reduced absorption of phenytoin or an increase in the rate of its metabolism and elimination.
Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinblastine sulfate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects. Enhanced toxicity has been reported in patients receiving concomitant erythromycin (see ADVERSE REACTIONS).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Aspermia has been reported in man. Animal studies suggest that teratogenic effects may occur. See WARNINGS regarding impaired fertility. Animal studies have shown metaphase arrest and degenerative changes in germ cells. Amenorrhea has occurred in some patients treated with the combination consisting of an alkylating agent, procarbazine, prednisone and vinblastine sulfate. Its occurrence was related to the total dose of these 4 agents used. Recovery of menses was frequent. The same combination of drugs given to male patients produced azoospermia; if spermatogenesis did return, it was not likely to do so with less than 2 years of unmaintained remission.

Mutagenicity
Tests in *Salmonella typhimurium* and with the dominant lethal assay in mice failed to demonstrate mutagenicity. Sperm abnormalities have been noted in mice. Vinblastine sulfate has produced an increase in micronuclei formation in bone marrow cells of mice; however, since vinblastine sulfate inhibits mitotic spindle formation, it cannot be concluded that this is evidence of mutagenicity.

Additional studies in mice demonstrated no reduction in fertility of males. Chromosomal translocations did occur in male mice. First-generation male offspring of these mice were not heterozygous translocation carriers.

*In vitro* tests using hamster lung cells in culture have produced chromosomal changes, including chromatid breaks and exchanges, whereas tests using another type of hamster cell failed to demonstrate mutation. Breaks and aberrations were not observed on chromosome analysis of marrow cells from patients being treated with this drug.

It is not clear from the literature how this drug affects synthesis of DNA and RNA. Some believe that there is no interference. Others believe that vinblastine interferes with nucleic acid metabolism but may not do so by direct effect but possibly as the result of biochemical disturbance in some other part of the molecular organization of the cell. No inhibition of RNA synthesis occurred in rat hepatoma cells exposed in culture to noncytotoxic levels of vinblastine. Conflicting results have been noted by others regarding interference with DNA synthesis.

Carcinogenesis
There is no currently available evidence to indicate that vinblastine sulfate itself has been carcinogenic in humans since the inception of its clinical use in the late 1950's. Patients treated for Hodgkin's disease have developed leukemia following radiation therapy and administration of vinblastine sulfate in combination with other chemotherapy including agents known to intercalate with DNA. It is not known to what extent vinblastine sulfate may have contributed to the appearance of leukemia. Available data in rats and mice have failed to demonstrate clearly evidence of carcinogenesis when the animals were treated with the maximum tolerated dose and with one-half that dose for 6 months. This testing system demonstrated that other agents were clearly carcinogenic, whereas vinblastine sulfate was in the group of drugs causing slightly increased or the same tumor incidence as controls in one study and 1.5 to 2-fold increase in tumor incidence over controls in another study.

**Pregnancy**

Teratogenic Effects; Pregnancy Category D
(See WARNINGS). Vinblastine sulfate should be given to a pregnant woman only if clearly needed. Animal studies suggest that teratogenic effects may occur.

**Pediatric Use**
The dosage schedule for pediatric patients is indicated under DOSAGE AND ADMINISTRATION.

**Nursing Mothers**
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from vinblastine sulfate in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

**ADVERSE REACTIONS**
*Prior to the use of the drug, patients should be advised of the possibility of untoward symptoms.*
In general, the incidence of adverse reactions attending the use of vinblastine sulfate appears to be related to the size of the dose employed. With the exception of epilation, leukopenia, and neurologic side effects, adverse reactions generally have not persisted for longer than 24 hours. Neurologic side effects are not common; but when they do occur, they often last for more than 24 hours. Leukopenia, the most common adverse reaction, is usually the dose-limiting factor.
The following are manifestations which have been reported as adverse reactions, in decreasing order of frequency. The most common adverse reactions are underlined:
**Hematologic:**Leukopenia (granulocytopenia), anemia, thrombocytopenia (myelosuppression).
**Dermatologic:**Alopecia is common. A single case of light sensitivity associated with this product has been reported.
**Gastrointestinal:**Constipation, anorexia, nausea, vomiting, abdominal pain, ileus, vesiculation of the mouth, pharyngitis, diarrhea, hemorrhagic enterocolitis, bleeding from an old peptic ulcer, rectal bleeding.
**Neurologic:** Numbness of digits (paresthesias), loss of deep tendon reflexes, peripheral neuritis, mental depression, headache, convulsions.
Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness which may be temporary or permanent, and difficulties with balance including dizziness, nystagmus, and vertigo. Particular caution is warranted when vinblastine sulfate is used in combination with other agents known to be ototoxic such as platinum-containing oncolytics.
**Cardiovascular:**Hypertension. Cardiac effects such as myocardial infarction, angina pectoris and transient abnormalities of ECG related to coronary ischemia have been reported very rarely. Cases of unexpected myocardial infarction and cerebrovascular accidents have occurred in patients undergoing combination chemotherapy with vinblastine, bleomycin, and cisplatin. Raynaud's phenomenon has also been reported with this combination.
**Pulmonary:** See PRECAUTIONS.

**Miscellaneous:** Malaise, bone pain, weakness, pain in tumor-containing tissue, dizziness, jaw pain, skin vesiculation, hypertension, Raynaud's phenomenon when patients are being treated with vinblastine sulfate in combination with bleomycin and cis-platinum for testicular cancer. The syndrome of inappropriate secretion of antidiuretic hormone has occurred with higher than recommended doses. Nausea and vomiting usually may be controlled with ease by antiemetic agents. When epilation develops, it frequently is not total; and, in some cases, hair regrows while maintenance therapy continues.
Extravasation during intravenous injection may lead to cellulitis and phlebitis. If the amount of extravasation is great, sloughing may occur.

## OVERDOSAGE

### Signs and Symptoms
Side effects following the use of vinblastine sulfate are dose-related. Therefore, following administration of more than the recommended dose, patients can be expected to experience these effects in an exaggerated fashion. (See CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) There is no specific antidote. In addition, neurotoxicity similar to that with vincristine sulfate may be observed. Since the major route of excretion may be through the biliary system, toxicity from this drug may be increased when there is hepatic insufficiency.

### Treatment
To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient. Overdoses of vinblastine sulfate have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered. Supportive care should include the following: (1) prevention of side effects that result from the syndrome of inappropriate secretion of antidiuretic hormone (this would include restriction of the volume of daily fluid intake to that of the urine output plus insensible loss and perhaps the administration of a diuretic affecting the function of the loop of Henle and the distal tubule); (2) administration of an anticonvulsant; (3) prevention of ileus; (4) monitoring the cardiovascular system; and (5) determining daily blood counts for guidance in transfusion requirements and assessing the risk of infection. The major effect of excessive doses of vinblastine sulfate will be myelosuppression, which may be life-threatening. There is no information regarding the effectiveness of dialysis nor of cholestyramine for the treatment of overdosage.
Vinblastine sulfate in the dry state is irregularly and unpredictably absorbed from the gastrointestinal tract following oral administration. Absorption of the solution has not been studied. If vinblastine is swallowed, activated charcoal in a water slurry may be given by mouth along with a cathartic. The use of cholestyramine in this situation has not been reported.
Symptoms of overdose will appear when greater-than-recommended doses are given. Any dose of vinblastine sulfate that results in elimination of platelets and neutrophils from blood and marrow and their precursors from marrow should be considered life-threatening. The exact dose that will do this in all patients is unknown. Overdoses occurring during prolonged, consecutive-day infusions may be more toxic than the same total dose given by rapid intravenous injection. The intravenous median lethal dose in mice is 10 mg/kg body weight; in rats, it is 2.9 mg/kg. The oral median lethal dose in rats is 7 mg/kg.
Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying if the drug has been swallowed. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

## DOSAGE AND ADMINISTRATION
*This preparation is for intravenous use only (see WARNINGS).*

### Special Dispensing Information
WHEN DISPENSING VINBLASTINE SULFATE IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN THE PROVIDED OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (see WARNINGS). A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, to state: "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY".
**Caution: It is extremely important that the intravenous needle or catheter be properly positioned before any vinblastine sulfate is injected. Leakage into surrounding tissue during intravenous administration of vinblastine sulfate may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and minimize discomfort and the possibility of cellulitis.**
There are variations in the depth of the leukopenic response which follows therapy with vinblastine sulfate. For this reason, it is recommended that the drug be given no more frequently than *once every 7 days*.

**Adult patients**

It is wise to initiate therapy for adults by administering a single intravenous dose of 3.7 mg/$m^2$ of body surface area (bsa). Thereafter, white-blood-cell counts should be made to determine the patient's sensitivity to vinblastine sulfate.

A simplified and conservative incremental approach to dosage *at weekly intervals* for adults may be outlined as follows:

First dose.....3.7 mg/$m^2$ bsa

Second dose.....5.5 mg/$m^2$ bsa

Third dose.....7.4 mg/$m^2$ bsa

Fourth dose.....9.25 mg/$m^2$ bsa

Fifth dose.....11.1 mg/$m^2$ bsa

The above-mentioned increases may be used until a maximum dose not exceeding 18.5 mg/$m^2$ bsa for adults is reached. The dose should not be increased after that dose which reduces the white-cell count to approximately 3000 cells/$mm^3$. In some adults, 3.7 mg/$m^2$ bsa may produce this leukopenia; other adults may require more than 11.1 mg/$m^2$ bsa; and, very rarely, as much as 18.5 mg/$m^2$ bsa may be necessary. For most adult patients, however, the weekly dosage will prove to be 5.5 to 7.4 mg/$m^2$ bsa.

When the dose of vinblastine sulfate which will produce the above degree of leukopenia has been established, a dose of *1 increment smaller* than this should be administered at weekly intervals for maintenance. Thus, the patient is receiving the maximum dose that does not cause leukopenia. *It should be emphasized that, even though 7 days have elapsed, the next dose of vinblastine sulfate should not be given until the white-cell count has returned to at least 4000/$mm^3$*. In some cases, oncolytic activity may be encountered before leukopenic effect. When this occurs, there is no need to increase the size of the subsequent doses (See PRECAUTIONS).

**Pediatric Patients**

A review of published literature from 1993 to 1995 showed that initial doses of vinblastine sulfate in pediatric patients varied depending on the schedule used and whether vinblastine sulfate was administered as a single agent or incorporated within a particular chemotherapeutic regimen. As a single agent for Letterer-Siwe disease (histiocytosis X), the initial dose of vinblastine sulfate was reported as 6.5 mg/$m^2$. When vinblastine sulfate was used in combination with other chemotherapeutic agents for the treatment of Hodgkin's disease, the initial dose was reported as

6 mg/$m^2$. For testicular germ cell carcinomas, the initial dose of vinblastine sulfate was reported as 3 mg/$m^2$ in a combination regimen. Dose modifications should be guided by hematologic tolerance.

**Patients with Renal or Hepatic Impairment**

A reduction of 50% in the dose of vinblastine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL. Since metabolism and excretion are primarily hepatic, no modification is recommended for patients with impaired renal function.

The duration of maintenance therapy varies according to the disease being treated and the combination of antineoplastic agents being used. There are differences of opinion regarding the duration of maintenance therapy with the same protocol for a particular disease; for example, various durations have been used with the MOPP program in treating Hodgkin's disease. Prolonged chemotherapy for maintaining remissions involves several risks, among which are life-threatening infectious diseases, sterility, and possibly the appearance of other cancers through suppression of immune surveillance.

In some disorders, survival following complete remission may not be as prolonged as that achieved with shorter periods of maintenance therapy. On the other hand, failure to provide maintenance therapy in some patients may lead to unnecessary relapse; complete remissions in patients with testicular cancer, unless maintained for at least 2 years, often result in early relapse.

To prepare a solution containing 1 mg/mL of vinblastine sulfate, add 10 mL of Bacteriostatic Sodium Chloride Injection (preserved with benzyl alcohol) or 10 mL of Sodium Chloride Injection (unpreserved) to the 10 mg of Vinblastine Sulfate for Injection in the sterile vial. Do not use other solutions. The drug dissolves instantly to give a clear solution.

Unused portions of the remaining solutions made with normal saline that do not contain preservatives should be discarded immediately. Unused preservative-containing solutions made with normal saline may be stored in a refrigerator for future use for a maximum of 28 days.

The dose of vinblastine sulfate (calculated to provide the desired amount) may be injected either into the tubing of a running intravenous infusion or directly into a vein. The latter procedure is readily adaptable to outpatient therapy. In either case, the injection may be completed in about 1 minute. If care is taken to insure that the needle is securely within the vein and that no solution containing vinblastine sulfate is spilled extravascularly, cellulitis and/or phlebitis will not occur. To minimize further the possibility of extravascular spillage, it is suggested that the syringe and needle be rinsed with venous blood before withdrawal of the needle. The dose should not be diluted in large volumes of diluent (i.e., 100 to 250 mL) or given intravenously for prolonged periods (ranging from 30 to 60 minutes or more), since this frequently results in irritation of the vein and increases the chance of extravasation.

Because of the enhanced possibility of thrombosis, it is considered inadvisable to inject a solution of vinblastine sulfate into an extremity in which the circulation is impaired or potentially impaired by such conditions as compressing or invading neoplasm, phlebitis, or varicosity.

*Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.*

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**HOW SUPPLIED**

Vinblastine Sulfate for Injection USP is supplied in packs of ten individually-boxed vials containing 10 mg lyophilized vinblastine sulfate.

**NDC 55390-091-10.**

Store vials in refrigerator, 2° to 8°C (36° to 46° F) to assure extended stability.

**REFERENCES**


1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253 (11) :1590-1592.

3. National Study Commission on Cytotoxic Exposure – Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia*, 1983; 1:426-428.

5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *CA – A Cancer Journal for Clinicians*, 1983; (Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J. Hosp Pharm*, 1990; 47:1033-1049.

7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J. Hosp Pharm*, 1986; 43:1193-1204.



Manufactured by:
Ben Venue Laboratories
Bedford, OH 44146
December 2001

Manufactured for:
Bedford Laboratories™
Bedford, Ohio 44146
VIN-P02